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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/898,556	07/03/2001	C. Frank Bennett	RTS-0248	2718

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Jane Massey Licata
Licata & Tyrrell, P.C.
66 East Main Street
Marlton, NJ 08053

EXAMINER
LACOURCIERE, KAREN A

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 11/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/898,556	BENNETT ET AL.	
	Examin r	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-10, 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

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DETAILED ACTION

Election/Restrictions

The amendment to claim 1, filed August 27, 2002, directs claims 1, 2, 4-10 and 12-15 to encompass an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 1 is directed to encompass antisense targeted to SEQ ID NO: 10 and SEQ ID NO: 11. As originally presented, the claims were drawn to antisense targeted to SEQ ID NO: 3. As amended, the claimed antisense, targeted to SEQ ID NO: 10 and 11, are considered to be unrelated to the originally presented invention, since each antisense to each target sequence claimed is structurally and functionally independent and distinct for the following reasons: each antisense sequence has a unique nucleotide sequence based on the target sequence, and the antisense targeted to the newly claimed sequences are to a different region of HKR1, for example, the antisense targeted to SEQ ID NO: 10 and 11 includes exon sequences which do not exist in the originally examined SEQ ID NO: 3. Furthermore, a search of more than one (1) of the target sequences claimed in claim 1 presents an undue burden on the Patent and Trademark Office due to the complex nature of the search and corresponding examination of more than one (1) of the claimed target sequences. Therefore, the amended claims will only be examined to the extent that they read on the invention which was elected by original presentation, antisense targeted to a nucleic acid encoding HKR1 wherein the nucleic acid is SEQ ID NO: 3.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for

prosecution on the merits. Accordingly, antisense targeted to SEQ ID NO: 10 and SEQ ID NO: 11 are withdrawn from consideration as being directed to a non-elected invention. Claims 1, 2, 4-10 and 12-15 will only be examined to the extent that they read on antisense targeted to SEQ ID NO: 3. See 37 CFR 1.142(b) and MPEP § 821.03.

A complete reply to the final rejection must include cancellation of nonelected subject matter or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The rejection of record of claims 1, 2, 4-10 and 12-20 under 35 U.S.C. 112, second paragraph, set forth in the prior Office action (mailed 05-29-02) is withdrawn in response to Applicant's amendments filed August 27, 2002.

The rejection of record of claims 15-20 under 35 U.S.C. 112, first paragraph, set forth in the prior Office action (mailed 05-29-02) is withdrawn in response to Applicant's amendments filed August 27, 2002.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 2, 4-10 and 12-15 are considered to be indefinite because they read on non-elected subject matter, specifically, antisense targeted to SEQ ID NO: 10 and 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4-10 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oguri et al. (reference AF on PTO form 1449, filed 07-03-01) in view of Taylor et al. (DDT, Vol. 4, No. 12, Dec. 1999), Milner et al. (Nature Biotechnology, Vol. 15, June 1997), and Baracchini et al. (US Patent No. 5,801,154).

Oguri et al. teach the full length sequence of a nucleic acid encoding HKR1, SEQ ID NO: 3 (see figure 1 of Oguri et al.), which includes the sequence of the coding region, the stop codon and the 3'-untranslated region. Oguri et al. teach that HKR1 (SEQ ID NO: 3) expression is induced by platinum drugs in human lung

adenocarcinoma cells, both *in vitro* and *in vivo*, but that the "functions of the HKR1 remain to be elucidated" (see page 66, first paragraph) and the role of HKR1 in platinum drug resistance or metabolism is uncertain. Oguri et al. teach, "Further studies are required to clarify the association between HKR1 mRNA overexpression and platinum drug resistance and/or metabolism". Oguri et al. do not teach antisense targeted to HKR1 mRNA, nor do they teach the modifications to antisense claimed.

Taylor et al. teach antisense as a research tool to elucidate the function of any gene of known sequence.

Milner et al. teach methods of making and screening antisense molecules against a desired target gene in any region of the gene, including the 3' untranslated region, the stop codon region or the coding region.

Baracchini et al. teach 2'-O-methoxyethyl sugar modifications, 5-methyl cytosine base modifications, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, to increase antisense stability and enhance affinity and teach antisense oligonucleotides of 8-30 nucleotides in length (see for example columns 6-9) and specifically teach targeting the coding region, translation stop codon region and the 3'-untranslated region of a target gene (see for example, column 9). Baracchini et al. further teach pharmaceutical carriers and colloidal dispersion systems (for example liposomes) for use in delivery of antisense compounds.

It would have been obvious to one of ordinary skill in the art, at the time the instant invention was made, to make an antisense molecule targeted to a nucleic acid encoding HKR1 (SEQ ID NO:3), including the coding region, translation stop codon

region or the 3'-untranslated region, based on the sequence taught by Oguri et al., because methods of making antisense targeted to a known gene, including the specific regions claimed, were well known in the art, as exemplified by Milner et al. It would have been obvious to make an antisense molecule targeted to the coding region, the translation stop codon region or the 3'-untranslated region because each of these regions was well known in the art as a region of a gene to target with antisense, as exemplified by Baracchini et al., and because these regions encompass the entire sequence taught by the art, Oguri et al. The art recognized antisense as a research tool, useful for clarifying the role of a gene, and Oguri et al. identified HKR1 as a target gene whose function was not well defined (see page 66, first paragraph, for example) and merited additional study because of its association with lung cancer cell response to platinum chemotherapy both *in vivo* and *in vitro* (see for example, p 66, third paragraph). It further would have been obvious to make such antisense of a length within the range of 8-50 nucleobases (as taught by Baracchini et al.), because antisense of a short length are more easily synthesized and easier to deliver to cells, and this size range was conventional in the art. It would have been further obvious to make said antisense comprising modifications, including 2'-O-methoxyethyl, 5-methyl cytosine, chimeric oligonucleotides and modified internucleoside linkages, including phosphorothioate linkages, as taught by Baracchini et al., because such modifications were routine and well known in the art as modifications which enhance the stability, uptake and affinity of an antisense molecule (see for example Baracchini et al. column 6, paragraph 3). It would have been obvious to one of ordinary skill in the art to make a

composition comprising said antisense and a pharmaceutically acceptable carrier, including a colloidal dispersion system, because pharmaceutically acceptable carriers, including colloidal dispersion systems (e.g. liposomes) were well known in the art for use with antisense molecules as a means to deliver antisense molecules to cells *in vitro* (cell culture), as evidenced by Baracchini et al.

One of ordinary skill in the art would have been motivated to make antisense targeted to HKR1 (SEQ ID NO: 3), because antisense was well known in the art as a means to selectively inhibit the expression of a gene and can be designed with minimal information (i.e. nucleotide sequence)(see for example Taylor, p 564, second column). The skilled artisan would have been motivated to make said antisense targeted to the coding region, translation stop codon region or the 3'-untranslated region based on the teachings of Baracchini, and because all of the sequence information available in Oguri et al. encompasses these regions. One of ordinary skill in the art would have been motivated to make antisense to HKR1 (SEQ ID NO: 3) to use *in vitro* in order to determine the role of HKR1 in the response to platinum therapeutics, because antisense would have selectively inhibited HKR1 and because the art did not provide any other type of inhibitor for HKR1, or enough information about HKR1 to design any other type of inhibitor. One of ordinary skill in the art would have been motivated to make such antisense 8-50 nucleotides in length and with the modifications and in the compositions taught by Baracchini et al. for the benefit of ease of delivery and synthesis, and to realize the benefits of improved stability and hybridization properties these modifications provided.

One skilled in the art would have expected to be able to find antisense which inhibits the expression of HKR1, including antisense targeted to the coding region, translation stop codon region, and the 3'-untranslated region, because the sequence of a nucleic acid encoding HKR1 (SEQ ID NO: 3) was known in the art, and the known sequence consists of these regions, and antisense could "be designed to inhibit any gene target provided that the sequence is known" (Taylor et al., p 562, column 1, second paragraph), methods of screening for antisense to a known gene was routine (see for example Milner et al.).

It would have been obvious to one of ordinary skill in the art to use antisense targeted to a nucleic acid encoding HKR1 in a method of inhibiting the expression of HKR1 (SEQ ID NO: 3) in cells *in vitro* (cell culture), including antisense targeted to the coding region, translation stop codon region and 3'-untranslated region, because it would be an obvious use for an antisense molecule designed to hybridize to and inhibit the expression of a nucleic acid encoding HKR1. One of ordinary skill in the art would have been motivated to use antisense targeted to a nucleic acid encoding HKR1 (SEQ ID NO: 3) to inhibit the expression of HKR1 in cells *in vitro* because the upregulation of HKR1 expression in cells treated with platinum *in vitro* was demonstrated to correlate with upregulation in cells treated with platinum *in vivo* and would have provided a model to study the role of HKR1 in cellular response to platinum.

Therefore, at the time the instant invention was made, the invention of claims 1, 2, 4-10 and 12-15, as a whole, would have been obvious to one of ordinary skill in the art.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Friday 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
November 15, 2002

SEAN McGARRY
PRIMARY EXAMINER